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09/580,523	05/30/2000	Xiao-Mai Zhou	A7483	8284

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/580,523	Zhou, X-M
Examiner	**Art Unit**
MINH TAM DAVIS	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 26, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above, claim(s) *4-9, 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 10, 13, 16, 19, 22, 25, and 28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Applicant's election of group I, claims 1-3, 10, 13, 16, 19, 22, 25 and 28 in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Accordingly, claims 1-3, 10, 13, 16, 19, 22, 25 and 28 are examined in the instant application.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the reasons:

Residues 71-89, and 143-168 in figure 3B legend on page 32 is not accompanied by a sequence identification number.

OBJECTION

The specification is objected to because the BH3 BAD sequence (SEQ ID NO:4 or BAD sequence in Figure 3A) does not seem to be corresponding to the residues 143-168 of SEQ ID NO:1, defined as BAD BH3 peptide in figure 3B legend on page 32.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-3, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1-3, 10, 13, 16, 19, 22, 25 and 28 are indefinite for the use of the language "substantially" in claims 1, 2, and 13. The term "substantially" in claims 1, 2, 13 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

2. Claims 1-3, 10, 13, 16, 19, 22, 25 and 28 are rejected as being indefinite for the use of designation "BH3" in claims 1 and 13 as the sole means of identifying the claimed peptide domain. The use of laboratory designation only to identify a particular peptide domain renders the claim indefinite because different laboratories may use the same laboratory designations to define completely distinct peptide domain. Amendment of the claims to include physical and/or functional characteristics of "BH3" which unambiguously define "BH3" is required.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are drawn to an isolated mutant polypeptide BAD or fragment thereof, which 1) contains a domain "substantially" identical to BH3 domain of a naturally-occuring or wild type mammalian BAD, 2) does not have a serine at a position corresponding to position 118 of SEQ ID NO:1, wherein said position is identified by alignment of said isolated polypeptide or fragment thereof to SEQ ID NO:1, and 3) has cell death

promoting activity. Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are further drawn to an isolated mutant polypeptide BAD or fragment thereof, which is "substantially" identical to SEQ ID NO:1.

Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 encompass any mutant of SEQ ID NO:1, or a polypeptide BAD with any mutation in the BH3 domain.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification discloses a mutation of murine BAD of SEQ ID NO:2, wherein the serine at position 155 is replaced by alanine, abolishes the phosphorylation of the murine BAD, and heterodimer formation with Bcl-X_L, and wherein serine 155 is located at the center of the BH3 domain, and phosphorylation of serine 155 promotes cell survival (Examples 1-2, on pages 72-77, and example 9 on pages 87-93). SEQ ID NO:1 is the human BAD, wherein the serine at position 118 correspond to the serine 155 of the murine BAD of SEQ ID NO:2 (p.7, and 40-41,

and table 1 on page 42). No further description of mutants by substitution is provided in the specification. The claims however read on mutants of SEQ ID NO:1, wherein said mutants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide of SEQ ID NO:1, or throughout the BH3 domain, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification and all other pending claims do not place any limit on the number of amino acids that could be substituted. Thus the scope of the claims includes numerous structural variants. Although the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated.. Structural features, that could distinguish the claimed variants from the polypeptide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed, because the function of a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to

disclose which amino acid(s) would be subjected to conservative substitution. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO:1 alone is insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants. Thus, applicant was not in possession of the claimed variants.

Thus, there is insufficient support of claims 1-2, 10, 13, 16, 19, 22, 25 and 28 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore, only a polypeptide comprising SEQ ID NO:1, wherein the serine 118 of SEQ ID NO:1 is mutated, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are drawn to an isolated mutant polypeptide BAD or fragment thereof, which 1) contains a domain substantially identical to BH3 domain of a

naturally-occuring or wild type mammalian BAD, 2) does not have a serine at a position corresponding to position 118 of SEQ ID NO:1, wherein "said position is identified by alignment of said isolated polypeptide or fragment thereof to SEQ ID NO:1", and 3) has cell death promoting activity.

The specification discloses a mutation of murine BAD of SEQ ID NO:2, wherein the serine at position 155 is replaced by alanine, abolishes the phosphorylation of the murine BAD, and heterodimer formation with Bcl-X_L, and wherein serine 155 is located at the center of the BH3 domain, and phosphorylation of serine 155 promotes cell survival (Examples 1-2, on pages 72-77, and example 9 on pages 87-93). SEQ ID NO:1 is the human BAD, wherein the serine at position 118 correspond to the serine 155 of the murine BAD of SEQ ID NO:2 (p.7, and 40-41, and table 1 on page 42). The specification further discloses mutants of BAD having a domain substantially similar to the BH3 domain, and an amino acid different from serine at a position corresponding to position 118 of SEQ ID NO:1, as identified by alignment of the mutant sequences with SEQ ID NO:1 (p. 10-17). No further teaching of how to align the mutant sequences with SEQ ID NO:1 is found in the specification.

One cannot extrapolate the teaching in the specification to the claims, because it is not clear what the points of references are for aligment of the claimed mutant sequences with SEQ ID NO:1 to identify an amino acid at a position corresponding to serine 118 of SEQ ID NO:1.

In view of the above, it would have been undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

If Applicant could overcome the above 112, first paragraph rejection, claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO:1, wherein the serine 118 of SEQ ID NO:1 is mutated, does not reasonably provide enablement for any mutant of said polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are drawn to an isolated mutant polypeptide BAD or fragment thereof, which 1) contains a domain "substantially" identical to BH3 domain of a naturally-occuring or wild type mammalian BAD, 2) does not have a serine at a position corresponding to position 118 of SEQ ID NO:1, wherein said position is identified by alignment of said isolated polypeptide or fragment thereof to SEQ ID NO:1, and 3) has cell death promoting activity. Claims 1-2, 10, 13, 16, 19, 22, 25 and 28 are further drawn to an isolated mutant polypeptide BAD or fragment thereof, which is "substantially" identical to SEQ ID NO:1.

The scope of the claims includes numerous structural mutants. Applicants have not shown how to make and use the claimed mutants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by

glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. In the absence of a source of method of making such mutants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-2, 10, 19, 22, 25 and 28 rejected under 35 U.S.C. 102(b) as being anticipated by PN=5,965,703.

Claims 1-2, 10, 19, 22, 25 and 28 are drawn to an isolated mutant polypeptide BAD or isolated or synthetic fragment thereof, which 1) contains a domain "substantially" identical to BH3 domain of a naturally-occuring or wild type mammalian BAD, which is SEQ ID NO:1, 2) does not have a serine, or glycine or alanine at a position corresponding to position 118 of SEQ ID NO:1, wherein said position is identified by alignment of said isolated polypeptide or fragment thereof to SEQ ID NO:1, and 3) has cell death promoting activity (claims 1, 19, 22, 28). Said mutant polypeptide BAD or fragment thereof binds Bcl-X_L and/or Bcl-2 (claim 10), and comprises the amino acid sequence corresponding to positions 103-123 of SEQ IS NO:1 (claim 25). Claims 1-2, 10, 19, 22, 25 and 28 are further drawn to an isolated mutant polypeptide BAD or fragment thereof, which is "substantially" identical to SEQ ID NO:1 (claim 2).

PN=5,965,703 teaches a sequence which is 75% similar to the claimed SEQ ID NO:1, from amino acid 1 to 168, i.e. the entire length of the claimed SEQ ID NO:1, wherein the amino acid at the position corresponding the amino acid position 118 of SEQ ID NO:1 is threonine,

under sequence similarity search (MPSRCH search report, 09-580523-1b-rai, pages 4-5, SEQ ID NO:3). PN=5,965,703 further teaches that the recited sequence of SEQ ID NO:3 is mouse Bcl-X_L and/or Bcl-2 associated death (BAD) promoting polypeptide (figure 2 legend on column 3), wherein the mouse BAD shares the highest degree of homology with other Bcl-2 related proteins in the region believed to contain the binding site with Bcl-X_L and Bcl-2 (column 6, second paragraph), and wherein members of the Bcl-2 family are able to bind Bcl-X_L and Bcl-2 (column 3, paragraph under detailed decription of the invention).

Given the polypeptide sequence taught by PN=5,965,703, one of ordinary skill in the art would immediately envision the claimed polypeptide.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

December 3, 2001